

## REMARKS

### **STATUS OF THE CLAIMS**

Claims 26, 28-31 and 33-44 are pending and were rejected under 35 U.S.C. § 103(a).

In view of the following remarks, Applicants respectfully request reconsideration of the application.

### **35 U.S.C. § 103**

All of the pending claims remain rejected as allegedly obvious over U.S. Patent No. 6,015,686 (hereinafter "Dubensky"); Cella et al. (hereinafter "Cella") and U.S. Patent No. 5,736,388 (hereinafter "Chada") and WO 90/14090 (hereinafter "Gillespie"). All references are applied as set forth in the previous Office Action.

Applicants traverse the rejection and supporting remarks.

With respect to the law governing obviousness, to support an obviousness rejection under 35 U.S.C. § 103, "all the claim limitations must be taught or suggested by the prior art." M.P.E.P. § 2143.03. In addition, "the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure." M.P.E.P. § 706.02I, emphasis added.

Furthermore, it is axiomatic that statements in the prior art must be considered in the context of the teaching of the entire reference, and that rejection of claims **cannot** be predicated on mere identification in a reference of individual components of claimed limitations. In this regard, the Federal Circuit has consistently reversed a finding of obviousness, even when all claimed elements are individually present in the references. *See, e.g., In re Kotzab* 217 F.3d 1365, 55 USPQ2d 1313, 1317 (CAFC 2000, emphasis added):

While the test for establishing an implicit teaching, motivation or suggestion is what the combination of these two statements [in the reference] would have suggested to those of ordinary skill in the art, the two statements cannot be viewed in the abstract. Rather, they must be considered in the context of the teaching of the entire reference. Further, a rejection **cannot** be predicated on the mere identification [in the reference] of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.

Thus, the burden remains on the Office to show particular findings must be presented as to why a skilled artisan, with no knowledge of the claimed invention, would have selected the components in the art for combination in the manner claimed.

Applicants submit that, in the pending case, the Office has merely identified individual components of the claims and, when viewed in context of the references as a whole, there is no motivation to combine the references to arrive at the claimed expression vectors.

As acknowledged by the Office, Dubensky does not teach or suggest expression vectors comprising (i) a promoter operably linked to a nucleic acid molecule which, when transcribed *in vivo*, forms double stranded self-complementing RNA and (ii) an RNA polymerase II promoter operably linked to a nucleic acid molecule that encodes an antigen from a pathogenic agent.

Despite this acknowledgment, it is asserted that Dubensky's teachings regarding using a vector to express multiple heterologous genes and Chada's teachings regarding use of multiple promoters to express multiple genes provides the requisite motivation to arrive at an expression vector comprising two promoters. *See*, Final Office Action, page 5, asserting that disclosure of expression vectors that express multiple heterologous genes provides "explicit motivation to express multiple heterologous genes of Dubensky from different promoters within the same construct."

In fact, Dubensky and Chada clearly use the term "gene" to refer to sequences that encode a polypeptide or sequences that prevent translation of existing RNA (*i.e.*, antisense RNA). Neither Dubensky nor Chada provide any incentive to provide expression vectors that express an antigen and a sequence that does not encode or protein or bind to existing RNA, namely a non-coding, self-complementing double-stranded RNA sequence. Accordingly, one of skill in the art would not be motivated to replace one of the multiple heterologous "genes" as described in Dubensky and/or Chada with a non-gene, non-antisense sequence, which when transcribed, forms non-coding, double stranded, self-complementing RNA, as claimed.

The Office's assertion that Dubensky's teachings at col. 23, lines 1-13 regarding antisense sequences provide further motivation to combine these teachings with Gillespie or Cella is in error. *See*, Final Office Action, pages 6-7:

The motivation for expression dsRNA in each of the following references is as follows: Dubensky teaches that double-stranded RNA increases the expression of gamma interferon and boosts the expression of MHC I antigens, see column 23, lines 1-13, Gillespie also teaches inducing the production of interferon by administering dsRNA, see claims 9-16 and Cella teach that double stranded RNA induces interferon, protects against cytopathic effects of a virus in dendritic cells and increased the capacity of dendritic cells to prime T cells, see the abstract and the first two paragraphs in the discussion section on page 826.

The Office has ignored the fact that the referenced passage in Dubensky is referring to antisense sequences that form double stranded RNA by complementation with mRNA transcripts already present in the cell. This passage in no way can be construed as teaching or suggesting expression of a sequence which forms double stranded RNA via self-complementation as set forth in the pending claims. Furthermore, since Dubensky teaches that antisense sequences (which are different than self-complementing sequences as claimed) fully serve the function of inducing gamma interferon production, there is no motivation to substitute self-complementing sequences into Dubensky's multiple gene expression vectors, particularly given the fact that none of the references suggest doing so.

The Examiner has also incorrectly asserted that Gillespie's production of dsRNA in a host cell system is "*in vivo*" transcription. (Final Office Action, pages 7 and 8). In fact, Gillespie and Cella do not teach *in vivo* transcription of dsRNA from an expression vector, which is a positively recited limitation of the claimed expression vectors. Rather, Gillespie teaches that dsRNA is formed *in vitro* using a host cell system and the dsRNA form is subsequently administered to a human "in need for such therapy." (claims 9-16 of Gillespie). Similarly, Cella teaches nothing whatsoever about expression vectors and, accordingly, cannot teach *in vivo* transcription of a sequence that forms self-complementing dsRNA, as claimed. Applicants cited the passage on page 5 of Gillespie in their previous Response to show that the dsRNA of this reference is not transcribed *in vivo*, not to show that dsRNA must necessarily be trimmed with RNase.

Without the benefit of Applicants' disclosure, the skilled artisan would have had no reason to replace Dubenksy's antisense sequences with sequences, which when transcribed *in vivo*, form self-complementing dsRNA. The skilled artisan would also not have had a reasonable expectation of success, given that the cited references do not teach or suggest the ability of

dsRNA to form self-complementing sequences *in vivo* when transcribed by themselves from a vector, let alone when transcribed from a vector that also comprises a sequence encoding an antigen.

Thus, the cited references, and state of the art as a whole, does not provide a reason to combine the individual elements of the claimed invention as set forth in the claims and a *prima facie* case of obviousness has not been (and indeed cannot be) presented by the Office. The alleged motivation to combine is not present because (1) expression of multiple heterologous genes as described in Dubensky and Chada does not relate to expression of a gene and a non-gene and (2) none of the references teach or suggest *in vivo* transcription of a sequence that forms dsRNA by self-complementation.

Thus, the cited combination is based on impermissible hindsight reconstruction. As stated by the Court of Appeals for the Federal Circuit *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988), one of the very cases cited by the Examiner on page 6 of the Final Office Action: “One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.” Accordingly, withdrawal of the rejection is respectfully requested.

**CONCLUSION**

In view of the foregoing amendments, Applicants submit that the claims are now in condition for allowance and request early notification to that effect.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §1.16, §1.17, and §1.21, which may be required by this paper, or to credit any overpayment, to Deposit Account No. 18-1648, referencing Atty. Docket No. 2300-1463.

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Date: May 25, 2005

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